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April 8, 1997

Assistant Commissioner for Patents
Washington, D.C. 20231

Case Number: 002
Inventor(s): ALAN A. RUBIN
Title: IMPROVEMENT IN TREATMENT OF PARKINSON'S DISEASE AND RELATED DISORDERS BY NOVEL FORMULATIONS OF THE COMBINATION CARBIDOPA-LEVODOPA

Transmitted herewith for filing is above-identified Nonprovisional patent application under 35 U.S.C. 111(a).

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Respectfully submitted,

Alan A. Rubin, Inventor

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Enclosures

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April 8, 1997
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Alan A. Rubin

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TITLE

IMPROVEMENT IN TREATMENT OF PARKINSON'S DISEASE AND RELATED DISORDERS BY NOVEL FORMULATIONS OF THE COMBINATION CARBIDOPA-LEVODOPA

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to an improvement in the treatment of Parkinson's disease and related disorders. More specifically, the present invention introduces novel formulations of the combination carbidopa and levodopa, the current mainstay of therapy.

Background and Prior Art

Parkinson's disease is associated with the depletion of dopamine from cells in the corpus striatum. Since dopamine does not cross the blood brain barrier and cannot therefore be used to treat Parkinson's disease, its immediate precursor, levodopa, is used instead because it penetrates the brain where it is decarboxylated to dopamine. But levodopa is also decarboxylated to dopamine in peripheral tissues and consequently only a small portion of administered levodopa is transported unchanged to the brain. This reaction can be blocked by carbidopa which inhibits decarboxylation of peripheral levodopa but cannot itself cross the blood brain barrier and has no effect on the metabolism of levodopa in the brain.

The combination of carbidopa and levodopa is considered to be the most effective treatment for symptoms of Parkinson's disease (The Medical Letter, 35:31-34, 1993). Nevertheless, certain limitations become apparent within two to five years of initiating combination therapy. As the disease progresses, the benefit from each dose becomes shorter ("the wearing off effect") and some patients fluctuate unpredictably between mobility and immobility ("the on-off effect"). "On" periods are usually associated with high plasma levodopa concentrations and often include abnormal involuntary movements, i.e., dyskinesias. "Off"

periods have been correlated with low plasma levodopa and bradykinetic episodes.

In an effort to reduce the occurrence of "wearing off" and "on-off" phenomena, a controlled release oral dosage combination was introduced with claims of slow and simultaneous release of carbidopa and levodopa from the formulation (US Patent Number 4,900,755 issued February 13, 1990). Data from clinical trials cited in the patent indicate that effective antiparkinson effects were achieved with fewer daily doses of the controlled release form as compared with the conventional combination.

Nevertheless, there remains a significant flaw in the therapeutic application of controlled release carbidopa-levodopa; that is the considerable delay in onset of action. Mean time to peak concentration in healthy elderly subjects was found to be two hours for controlled release carbidopa-levodopa and only 0.5 hours for the conventional form (Physicians Desk Ref., 47th Ed., p. 976, 1993). A controlled release dosage form that could also provide rapid onset of action, at least equivalent to that of conventional carbidopa-levodopa would have an obvious clinical advantage over current therapy.

The strategy proposed in the present invention is to formulate oral dosage forms containing both immediate release carbidopa-levodopa and controlled release carbidopa-levodopa. Ingestion would provide rapid onset antiparkinson activity via the immediate release component followed by sustained therapeutic activity from the controlled release component.

SUMMARY OF THE INVENTION

It is the purpose and principal object of this invention to provide an improved method for the treatment of Parkinson's disease by using novel formulations of the combination carbidopa-levodopa which a) are effective in preventing the symptoms of Parkinson's disease and yet which b) act rapidly avoiding significant onset delay common to the standard controlled release therapy.

DETAILED DESCRIPTION

The novel oral dosage formulations of the present invention each contain immediate release and controlled release components of the antiparkinson agents carbidopa (5-200 mg) and levodopa (25-600 mg). The conventional immediate release combination of carbidopa-levodopa reaches peak plasma concentrations in 30 minutes whereas the onset of the controlled release component is two hours followed by prolonged release over a four- to six-hour period.

The usual daily therapeutic dose of levodopa, when administered with carbidopa, is 300 to 750 mg and the dose of carbidopa approximately 75 mg per day but the latter is apparently devoid of adverse effects even at doses of 400 mg per day (J. E. Ahlskog, Hosp. Form., 27:146, 1992). Although the optimum daily dosage of carbidopa-levodopa must ultimately be determined by titrating each patient, a preferred range for twice daily maintenance therapy may include immediate release of 10-25 mg carbidopa and 50-200 mg levodopa and sustained release of 25-75 mg carbidopa and 100-400 mg levodopa.

Specific examples of these formulations are cited below. The amount and excipients listed can be changed through methods known to those skilled in the preparation of immediate and sustained release dosage forms. Some of these methods are available in Remington's Pharmaceutical Sciences, 17th Ed., 1985, a standard reference in the field.

EXAMPLE 1

A two compartment tablet consisting of a core layer of sustained release carbidopa-levodopa overcoated with a layer of immediate release carbidopa-levodopa. The core ingredients are blended separately (as are the outer layer ingredients), compressed to produce core tablets and then overcoated with the compressed outer layer blend using a suitable coating press.

Ingredient	Mg per Tablet
Outer Layer (Immediate Release)	
Carbidopa	25.0
Levodopa	100.0
Microcrystalline Cellulose	224.0
Croscarmellose Sodium	15.0
Silicon Dioxide	3.0
Magnesium Stearate	3.0
Core Layer (Sustained Release)	
Carbidopa	50.0
Levodopa	200.0
Methocel E4M Premium CR	80.0
Microcrystalline Cellulose	61.0
Silicon Dioxide	2.0
Magnesium Stearate	2.0

EXAMPLE 2

A bilayer or multilayer tablet consisting of one layer of sustained release carbidopa-levodopa either adjacent to a layer of immediate release carbidopa-levodopa or separated by an additional excipient layer. The ingredients from each layer are blended separately, then compressed to produce a layered tablet using a suitable layered press.

Ingredient	Mg per Tablet
Layer 1 (Immediate Release)	
Carbidopa	12.5
Levodopa	50.0
Microcrystalline Cellulose	123.5
Silicon Dioxide	2.0
Magnesium Stearate	10.0
Layer 2 (Sustained Release)	
Carbidopa	37.5
Levodopa	150.0
Methocel E4M Premium CR	80.0
Microcrystalline Cellulose	53.5
Silicon Dioxide	2.0
Magnesium Stearate	2.0

EXAMPLE 3

An oral dosage form, such as a capsule or compressed tablet, containing immediate and sustained release carbidopa-levodopa pellets prepared by the following methods:

1. Dissolve Povidone in isopropyl alcohol (10% w/w)
2. Disperse micronized carbidopa and levodopa in Povidone solution
3. Layer the slurry from step 2 onto sugar spheres to form core pellets using a fluid-bed with a Wurster air suspension coating column
4. Dissolve ethyl cellulose and polyethylene glycol 4000 in methylene chloride and methanol (4:1) mixture (5% w/w)
5. Coat pellets from step 3 with polymer solution from step 4 in a fluid-bed with a Wurster air suspension coating column.

Appropriate amounts of uncoated core pellets containing immediate release carbidopa-levodopa (step 3) and polymer coated pellets containing sustained release carbidopa-levodopa (step 5) are included in an oral dosage form to provide the desired ratio of immediate and sustained release carbidopa-levodopa.

Ingredient	% by Weight
Uncoated Core Pellets (Immediate Release)	
Carbidopa	12.5
Levodopa	50.0
Povidone (K-30)	17.5
Sugar Spheres (35-40 Mesh)	20.0
Coated Pellets (Sustained Release)	
Core Pellet	94.0
Ethyl Cellulose	4.5
Polyethylene Glycol 4000	1.5

002

CLAIMS

What is claimed is:

1. A method for treating Parkinson's disease using an oral dosage formulation comprising an immediate release layer of 10-25 mg of carbidopa and 50-200 mg of levodopa and a sustained release layer of 25-75 mg of carbidopa and 100-400 mg of levodopa whereby, following administration, carbidopa and levodopa are available for rapid and sustained therapeutic action.

2. A method as claimed in Claim 1 characterized by a sustained release core depot of carbidopa-levodopa overcoated by an immediate release layer of carbidopa-levodopa.

3. A method as claimed in Claim 1 characterized by a multilayer tablet comprising at least one layer of sustained release carbidopa-levodopa adjacent to at least one layer of immediate release carbidopa-levodopa.

4. A method of Claim 3 wherein the layers in the tablet are separated by an excipient layer.

5. A pharmaceutical composition in oral dosage form for treating Parkinson's disease comprising a combination of an immediate release portion of a combination of carbidopa and levodopa and a sustained release portion of a combination of carbidopa and levodopa, the composition effective in treating Parkinson's disease, and a pharmaceutically acceptable vehicle, and whereby the carbidopa and levodopa are available for immediate and sustained therapeutic action upon administration.

6. The pharmaceutical composition of Claim 5 wherein the dosage form comprises a sustained release core portion of carbidopa and levodopa overcoated by an immediate release layer of carbidopa and levodopa.

7. The pharmaceutical composition of Claim 5 wherein the dosage form comprises a multilayer tablet comprising at least one layer of sustained release carbidopa-levodopa adjacent to at least one layer of immediate release carbidopa-levodopa.

8. The pharmaceutical composition of Claim 5 wherein the immediate release portion comprises about 10-25 mg of carbidopa and 50-200 mg of levodopa and a sustained release portion of about 25-75 mg of carbidopa and 100-400 mg of levodopa.

9. The pharmaceutical composition of Claim 8 wherein the dosage form comprises a sustained release core portion of carbidopa-levodopa overcoated by an immediate release layer of carbidopa-levodopa.

10. The pharmaceutical layer of Claim 8 wherein the dosage form comprises a multilayer tablet of at least one layer of sustained release carbidopa-levodopa adjacent to at least one layer of immediate release carbidopa-levodopa.

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TITLE

IMPROVEMENT IN TREATMENT OF PARKINSON'S DISEASE AND RELATED DISORDERS BY NOVEL FORMULATIONS OF THE COMBINATION CARBIDOPA-LEVODOPA

ABSTRACT

An oral antiparkinson drug delivery system consisting of carbidopa and levodopa in immediate and sustained release compartments provides a significant clinical advantage over currently available carbidopa-levodopa preparations.

Rev. 06/95

Docket Number
002

DECLARATION and POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVEMENT IN TREATMENT OF PARKINSON'S DISEASE AND RELATED DISORDERS BY NOVEL FORMULATIONS OF THE COMBINATION CARBIDOPA-LEVODOPA

the specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as U.S. Application No. _____ or PCT International Application No. _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Application No.	Country	Filing Date	Priority Claimed (Yes/No)

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States Provisional Application(s) listed below.

U.S. Provisional Application No.	U.S. Filing Date

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International Application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application or PCT International Application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is known to me to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application No.	Filing Date	Status (patented, pending or abandoned)

POWER OF ATTORNEY: I hereby appoint the following attorney(s) and/or agent(s) the power to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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